

LOADING CAPACITY AND RELEASE PROPERTY OF
PIPERINE LOADED SILICA AEROGEL AND SILICA XEROGEL

NURUL HIDAYAH MOHD YUNOS

UNIVERSITI TEKNOLOGI MALAYSIA

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NURUL HIDAYAH MOHD YUNOS

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To my beloved mother and father

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ABSTRACT

The feasibility of silica matrix as an oral drug delivery carrier for natural product was explored. Piperine was loaded into silica aerogel and xerogel via three different methods; impregnation, physical mixing and direct synthesis. Fourier-transform infrared (FTIR) and ultraviolet-visible (UV-Vis) spectroscopies results strongly indicated that no detectable drug degradation had occurred during the loading procedure. Brunauer-Emmett-Teller surface analysis (BET), X-ray diffraction (XRD), and field-emission scanning electron microscopy (FESEM) results indicated the successful loading of piperine into silica matrices. XRD results show the amorphization of piperine crystals after loading process with silica aerogel or xerogel, indicating the increment in the specific surface area of the drug. The degree of crystallinity of piperine loaded silica aerogel is extremely low compared to piperine-xerogel formulations. UV-Vis spectroscopy analysis revealed that the amount of piperine loaded was higher in silica aerogel than silica xerogel. This was due to the larger pore and higher surface area of silica aerogel compared to silica xerogel. Investigation on the release profile of piperine from loaded silica matrices in simulated gastric and intestinal fluids found that piperine loaded silica matrices dissolve faster than crystalline drug due to increase in specific surface area and non crystallinity state of the system. Piperine loaded silica aerogel gave the fastest dissolution (up to 100%), followed by piperine-xerogel (up to 45%) and crystalline piperine (< 5%). Formulations prepared via direct synthesis showed the fastest release, followed by impregnated and physically mixed systems. The ease in collapse of the silica matrices structure in water was observed to favor a faster release.

ABSTRAK

Kajian telah dijalankan terhadap keupayaan matriks silika sebagai pembawa dalam sistem penyampaian ubat oral bagi hasilan semulajadi. Piperina dimuatkan ke dalam silika aerogel dan xerogel menggunakan tiga kaedah; pengisitepuan, pencampuran fizik dan sintesis langsung. Data analisis spektroskopi inframerah transformasi Fourier (FTIR) dan ultralembayung-nampak (UV-Vis) menunjukkan tiada degradasi ubat berlaku semasa prosedur pemuatan. Data analisis permukaan Brunauer-Emmett-Teller (BET), pembelauan sinar-X (XRD) dan mikroskopi imbasan elektron pancaran medan (FESEM) menunjukkan piperina telah berjaya dimuatkan ke dalam matriks silika. Kajian XRD menunjukkan pengamorfusan hablur piperina selepas proses pemuatan terhadap silika aerogel dan xerogel yang menunjukkan peningkatan dalam luas permukaan spesifik ubat tersebut. Darjah kehabluran silika aerogel termuat piperina adalah sangat rendah berbanding formulasi piperina-xerogel. Analisis spektroskopi UV-Vis menjelaskan bahawa kuantiti piperina adalah lebih tinggi di dalam silika aerogel berbanding silika xerogel. Ini disebabkan saiz liang yang lebih besar dan luas permukaan yang lebih tinggi dalam silika aerogel berbanding silika xerogel. Kajian terhadap profil pelepasan piperina daripada matriks silika di dalam simulasi bendalir gastrik dan usus menunjukkan bahawa matriks silika termuat piperina larut lebih pantas berbanding hablur ubat disebabkan peningkatan dalam luas permukaan dan sifat bukan hablur sistem tersebut. Silika aerogel termuat piperina memberikan pelarutan paling pantas (sehingga 100%), diikuti oleh piperina-xerogel (sehingga 45%) dan hablur piperina (<5%). Formulasi yang disediakan dengan kaedah pemuatan langsung menunjukkan pelepasan paling cepat, diikuti oleh kaedah pengisitepuan dan pencampuran fizik. Struktur matriks silika yang mudah terurai di dalam air menggalakkan pelepasan.

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LIST OF ABBREVIATIONS

BET	-	Brunauer Emmett and Teller
DDC	-	drug delivery carrier
DDS	-	drug delivery system
FESEM	-	field emission-scanning electron microscopy
FTIR	-	Fourier transform infrared
GRAS	-	Generally Recognised as Safe
H ₂ SO ₄	-	sulphuric acid
KBr	-	potassium bromide
MCM	-	Mobil Crystalline of Materials
N ₂	-	nitrogen gas
Na ₂ SiO ₃	-	sodium silicate
NaOH	-	sodium hydroxide
NCPE	-	nanocomposite polymer electrolytes
NOAEL	-	no observed adverse effect level
OTC	-	over-the-counter
RHA	-	rice husk ash
RH	-	rice husk
SA	-	silica aerogel
SBA	-	Santa Barbara Amorphous type materials
SCF	-	supercritical fluid
SiO ₂	-	silicon dioxide, silica
SX	-	silica xerogel
TEOS	-	tetraethyl orthosilicate
TMOS	-	tetramethyl orthosilicate
TUD-1	-	Technische Universiteit Delft mesoporous silica materials

USA	-	United States of America
US\$	-	United States Dollar
US FDA	-	United States' Food and Drug Administration
UV-Vis	-	ultraviolet-visible
WHO	-	World Health Organization
XRD	-	X-ray diffraction
Rpm	-	round per minute
PGA	-	phenylglycine amide enzymes

LIST OF SYMBOLS

C	-	concentration
D	-	diffusion coefficient
g	-	gram
h	-	thickness of diffusion layer
h	-	Planck's constant
k	-	force constant
k'	-	dielectric constant
K	-	Kelvin
m	-	meter
n	-	diffraction order
λ	-	wavelength
$^{\circ}\text{C}$	-	degree Celsius
Pa	-	Pascal
P_c	-	critical pressure
S_{BET}	-	BET surface area
T	-	temperature
t	-	time
T_c	-	critical temperature
ν	-	vibrational energy level
W	-	Watt
θ	-	diffraction angle

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CHAPTER I

INTRODUCTION

1.1 General

The word medicine is derived from the Latin *ars medicina*, meaning the art of healing. When it comes to art, it may represent different approaches, sources, process, and belief in diagnosing, preventing and curing illness. Generally, medicine is described as a discipline devoted to understanding and treating disease, often referring to physical and chemical mechanisms [1]. Specifically, medicine means a substance or mixture of substances used in restoring or preserving health. Early records on medicine have been discovered from early traditional Chinese medicine, Indian Ayurveda, Arab Unani medicine, the Americas and ancient Greek medicine [2]. Historically, these ancient treatments include plants, animal parts, minerals and non-medication therapies. The revelation of the mysteries and mystiques in these ancient treatments through science and technology has led to the discoveries and innovations in modern drug delivery system.

According to World Health Organization (WHO), about three-quarters of the world population relies on the traditional remedies for their primary health needs. In Malaysia, an estimated US\$ 500 million is spent annually on traditional medicine

compared to about US\$ 300 million on allopathic medicine [2]. However, plant-derived products are preferred and have dominated the human pharmacopoeia for thousand of years almost unchallenged [3]. About 25% of modern medicines are made from plants, first used traditionally [4]. The rising concern on the safety and efficacy of plant-derived drug has ignited massive volume of research in this field.

1.2 Natural Product as Modern Medicine

A resurgence of interest in the study of medicinal plants has been taking place during the last decades. The world market for herbal medicines based on traditional knowledge is estimated at US\$ 60 thousand million in 2005 [5]. Traditional herbal remedies also remain a very important part of life in Asian markets such as China, Japan, and India. In Japan, 60-70% of allopathic doctors prescribe kampo medicines (Japanese herbal medicines) for their patients [2, 6]. In Malaysia, traditional forms of Malay, Chinese and Indian medicine are used extensively.

Despite of fast pace in medical advances, consumer in West are turning to alternative remedies such as herbals in increasing numbers, due to factors such as ageing populations, escalating healthcare costs, and trend towards self care [7, 8]. For example, in United States of America (USA) alone, herbal sales increased by 101% in mainstream markets between May 1996 and May 1998. Natural ingredients are also being incorporated increasingly into conventional prescription and over-the-counter (OTC) medicines as research continues into the safety and efficacy of new and known substances [9, 10].

1.3 Drug Delivery Carriers

In pharmaceutical field, the drug delivery carriers (DDC) serve as mechanisms to improve the delivery and effectiveness of drugs. It is advantageous to use drug carrier than pure drugs since DDC can decrease drug metabolism and reduce the toxicity of drugs [11]. DDC can also increase drug absorption and improve its release profile. As well as the active ingredient, the conventional tablet may contain inactive ingredients, or excipients, which are used in the delivery of each therapeutic product, such as filler, binder, colour and flavour to ensure that the tablet is easy to use and of a high quality [12]. The following pie chart (1.1) shows the typical contents of a tablet, while Table 1.1 describes their function in a drug formulation [13].

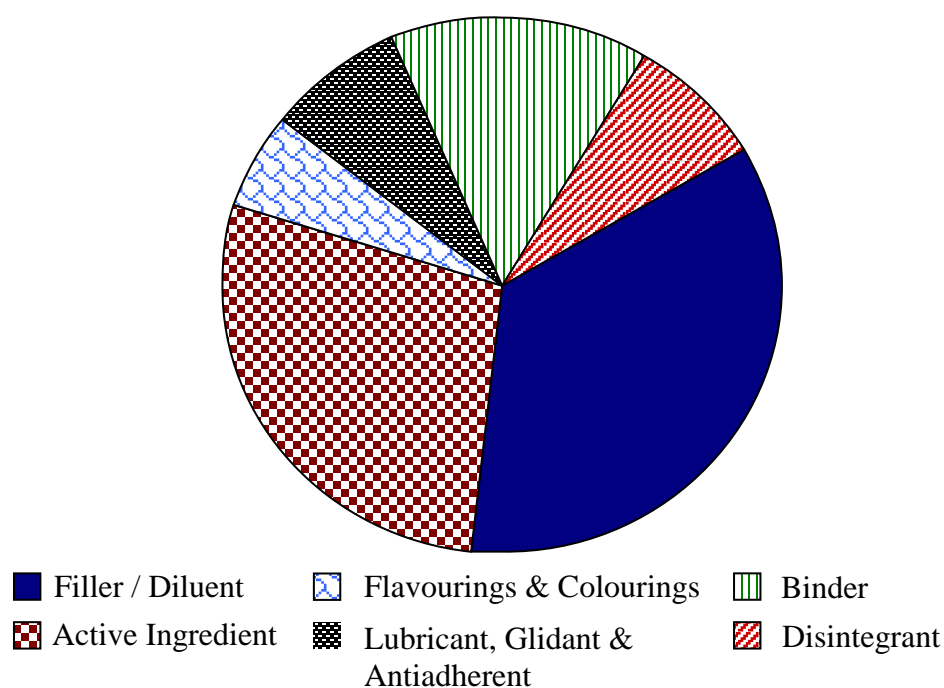


Figure 1.1 Typical contents of a conventional tablet

Table 1.1: Tablet excipients and their uses [13]

Excipients	Function
Filler (or diluent)	Filler, such as sucrose or lactose, is included to increase the size of the tablet. This is necessary as often the amount of 'active' is so tiny that the tablet would be too small to handle without it.
Disintegrant	Disintegrants help the tablet to break down into small fragments, when it is ingested. This helps the medicine to dissolve and be taken up by the body so that it can act more quickly. Disintegrants may include potato or cocoa butter.
Binder	A binder, such as glucose or sucrose, is added to hold the tablet together after it has been compressed, stopping it from breaking down into its separate ingredients.
Glidant	The glidant helps to keep the powder making up the tablet flowing as the tablet is being made, stopping it from forming lumps.
Lubricant	Lubricants ensure that the tablet has a smooth surface and that the powder does not stick to the equipment used to make the tablet.
Antiadherent	The antiadherent also stops the powder from sticking to the equipment as the tablet is being made.
Flavour	Flavouring agents help to make the tablet taste better.
Colourant	Colours are added to help you to recognize your tablet and to make it easier to take your medicine correctly.

1.4 Nanotechnology in Drug Delivery System

Nanotechnology has impacted and led significant advances in many fields. It is defined as that area of science and technology where dimensions and tolerance are in the range of 1.0 nm to 100 nm [14, 15]. It is also defined by Bawa *et al.* as the design, characterization, production, and application of structures, devices, and systems by controlled manipulation of size and shape at the nanometer scale (atomic,

molecular, and macromolecular scale) that produces structures, devices, and systems with at least one novel/superior characteristic or property [16]. Nanotechnology based tools and techniques are expected to create innovations and play critical role in mainstream biomedical applications including in drug delivery, imaging, and novel drug discovery techniques [17].

One of the important areas of nanotechnology is nanomedicine, which refers to highly specific medical intervention at the molecular scale for diagnosis, prevention, and treatment of disease [18]. The overall goal of nanomedicine is the same as it always has been in medicine; to diagnose as accurately and early as possible, treat as effectively as possible without side effects, and evaluate the efficacy of treatment invasively. By manipulating drugs and other materials at the nanometre scale, the fundamental properties and bioactivity of materials can be altered.

Nano-enabled drug delivery system (DDS) has led the development in medicine for improving the efficiency of drug and targeting aimed point of diseases. This is demonstrated by the fact that approximately 13% of the current global pharmaceutical market is related to the products incorporating a drug delivery system [19, 20]. The global pharmaceutical market was estimated at about US\$406 billion in 2002 and expected to grow more than double in value to US\$ 1.3 trillion by 2020 [21, 22].

There has been considerable interest in developing biodegradable nanoparticles as effective drug delivery devices. Nanoparticles are solid, colloidal particle consisting of macromolecular substances that vary in size from 10 nm to 1000 nm [23]. In nano-enabled drug delivery system, the drug of interest is dissolved, entrapped, adsorbed, attached, or encapsulated into/onto the nanoparticles matrix. The advantages of using nanoparticles for drug delivery are due to their three main properties:

- **Nano-scale:** because of their small size, they can penetrate through smaller capillaries and are taken up by cells, which allow efficient drug accumulation at the target sites.
- **High surface area:** the dissolution rate of drug depends on its surface area and solubility. Higher surface area allows more contact with the dissolution medium.
- **Biodegradable:** allows sustained drug release within target site over a period of days or even weeks.

Nanoparticulate drug delivery carriers allow for faster drug absorption, controlled dosage releases, and shielding from the body's immune system which enhance the effectiveness of already existing drugs [16, 24]. Silica aerogel and silica xerogel, silica matrices made by the sol gel process have emerged as ideal carrier materials for drug delivery system. The use of silica in delivery system can provide several benefits:

- High surface areas provide the possibility of high drug loadings in the matrix and thus increase the rate of reaction;
- The open pore morphology of silica matrices allow substrates to quickly move into the interior regions of the particle;
- Solvents used in the processing of the silica materials are environmentally friendly;
- Silica has been widely used as excipients in pharmaceutical industry.

1.5 Problem Statement

Since last decades, most drugs have been prepared in designed form to ensure for accurate dosage and convenience for drug administration. There has been a

dramatic increase in the awareness of continuous, prolonged, controlled-release medication. This is due to many of original controlled-released system is administered in high dose at a given time only and have to repeat that dose several hours or days later. This is not economical and sometimes results in damaging side effect [25]. Furthermore, the drug release rate is hard to control due to different properties of the drugs. Normally, the release rate is whether too slow for crystalline and/or too fast for amorphous drug [26-27]. Amorphous form due to absence of an ordered crystal lattice requires minimal energy and thus provides maximal solubility advantage as compared to the crystalline and hydrated form of drug.

In this research, piperine (5-benzo[1,3]dioxol-5-yl-1-piperidin-1-yl-penta-2,4-dien-1-one) is chosen as model drug due to its availability and commercial value in Malaysia. Piperine is naturally occurring in black pepper plant, *Piper nigrum* Linn with a yield of 35-55 % of its oleoresin [28]. Piperine has been evaluated by Food and Agriculture Organization of United Nations and World Health Organization (WHO) which indicated that piperine is safe to be used as food and flavouring agents [29]. It has been used as Ayurvedic and Chinese traditional medicine for a long time. Besides, there has been strong growth in sales of product that all-natural or a high proportion of pure, natural ingredients, especially in food, pharmaceutical and cosmetic products [7].

In comparison to ground spice, piperine is hygienic, concentrated and can be standardized for acceptable dosage [28]. However, piperine is a poor soluble drug and practically insoluble in water resulting in a poor absorption from gastrointestinal tract [30, 31]. It also exhibits sensitivity to light and oxygen that can undergo hydrolysis to piperidine and piperinic acid and also photolysis to *iso*-chavicine which lacks the pepper characteristics. Besides, if piperine were to remain captive in the form of raw black pepper, it will take time for its bioavailability enhancing property to be released [32]. In market, Bioperine®, a standardized piperine extract has been patented and claimed to exhibit bioavailability enhancer property to other nutrients [33]. However, the formulation of this supplement may contain several excipients, such as protein, carbohydrates, sugar, calcium carbonate, talc, magnesium stearate,

starch-gelatine paste, and diluents. The use of too many components has involved several different steps that could subsequently lead into troublesome production.

Excipients package active ingredient into discrete amounts that are easy to handle, give medications a specific look and colour for branding purposes, or imbue unpleasant-tasting medication to help with patient compliance, among hundreds of other uses [34]. On the other hand, some consumers or patients have suffered of being allergic to these additives that commonly appear in many medications [35]. For example, people who have difficulty digesting starch might react to tablets and capsules in which starch is the filler or binder. Others may be allergic to certain artificial colours used in producing medicine preparation. In more serious case, inappropriate use of talc or magnesium silicate as filler in drug tablets can lead to severe pulmonary toxicological responses [36]. Increasing number of allergy incidences along with rising concerns over ingredient safety in medicinal products must be taken into account in designing drug delivery system.

In order to overcome these problems, silica aerogel and xerogel maybe loaded with piperine via different methods. To the best of our knowledge, there is no report on silica matrices loaded with piperine. This may avoid the use of other excipients as these silica matrices could act as the filler and binder themselves. The loading of drug with silica matrices is expected to increase the dissolution rate and stability of piperine by increasing its surface area and wettability, while protecting piperine against destructive changes [28, 37]. In drug delivery system, the dissolution rate and solubility of poorly soluble drugs should be improved for desired overall performance of the system because a low dissolution rate resulting in poor absorption from the gastrointestinal tract [38]. Estimates by the pharmaceutical companies are that about 40% of the potential drugs are poorly soluble in water [39]. In previous studies, the use of nanoparticles as the drug delivery carriers has proven that they could accelerate the release rate of many kind of drugs [40-44].

The use of silica matrices such as silica aerogel, and silica xerogel as the drug delivery carriers have been explored recently. The feasibility of silica aerogels as drug delivery system was recently reported [45-47]. It was found that no degradation occurred during loading process via adsorption method using a low temperature supercritical extraction unit [46]. The enhancement in dissolution rate of drug loaded silica aerogel compared to crystalline drug was reported [45-47]. On the other hand, the drug loading is limited. Previous studies showed the potential of silica xerogel as the delivery system for the controlled release of various kinds of drugs [48-51]. However, the high density and limited surface area of silica xerogel has somehow limited its potential. Besides, in most of the previous studies, an orthosilicate such as tetramethyl orthosilicate (TMOS) or tetraethyl orthosilicate (TEOS) was used as silica source in preparing silica monoliths containing loaded drugs [47-51]. On the other hand, a new aqueous route for synthesis of silica monoliths that used commercially available sodium silicate as a precursor has been developed. However, alkoxysilanes and the commercially available sodium silicate are usually too expensive that silica aerogel production in an industrial scale is not economically practical. In order to overcome these problems, a modified aqueous route for synthesis of silica monoliths using rice husk ash as the cheap silicon source for production of pure silicate solution as a precursor was developed.

1.6 Objectives of Research

The objectives of this research are:

1. To synthesize and characterize piperine loaded silica matrices.
2. To determine the loading capacity and the drug release rate of the newly designed nano-enabled of drug delivery system.
3. To investigate the influences of synthesis conditions on the loading and release property of piperine.

1.7 Scope of Research

The silica matrices (silica aerogel and silica xerogel) were synthesized via sol-gel process using rice husk ash as silica source, followed by the loading of drug via different methods which are:

- Physical mixing (co-grinding)
- Impregnation
- Direct synthesis

Then, all samples are characterized for structural analysis using Fourier transform infrared spectroscopy (FTIR), Ultra-Visible spectroscopy (UV-Vis), and X-ray diffraction (XRD). The morphology and pore characteristics of the samples are analysed using field emission scanning electron microscopy (FESEM) and BET surface area analyzer, respectively. Meanwhile, the drug loading and its release rate investigation is carried out using UV-Vis spectroscopy. The research programme is designed according to the methodology outlined in the scheme as shown in Figure 1.2.

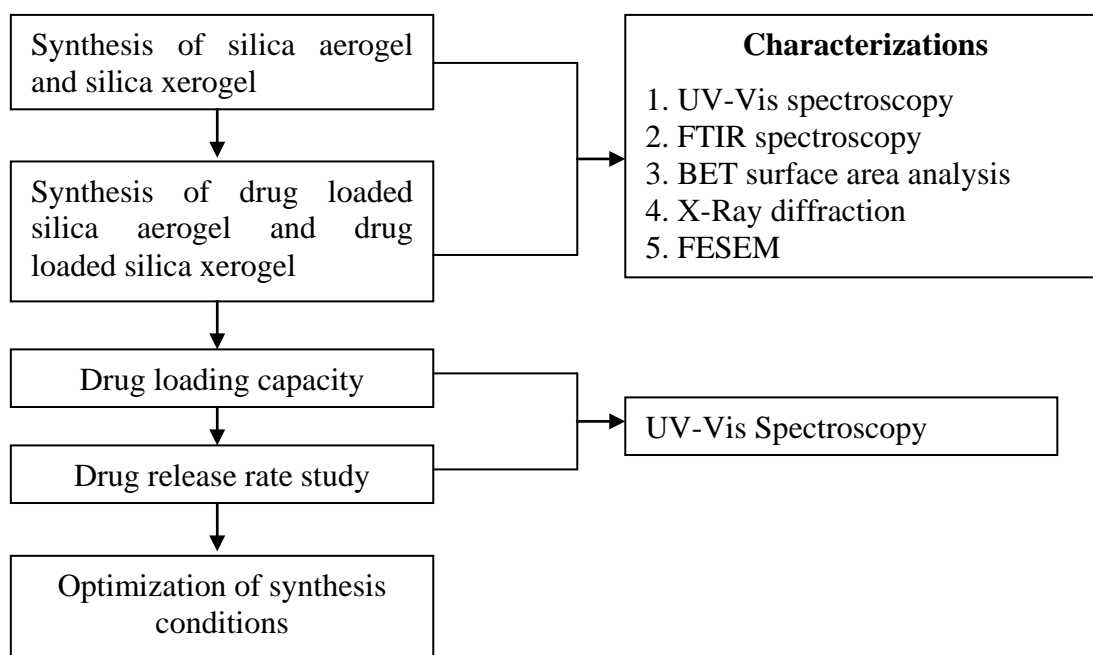


Figure 1.2 Flow diagram of research activities